Topics in Lupus Nephritis

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Conflict of interest statement: I do NOT receive research funding, payments or honoraria from any pharmaceutical company
Glomerular Capillary: Scanning EM

Welsch & Saleem, Nat Rev Nephrol 2011
Haraldsson Physiol Rev 2008
Frequency and Outcome of Lupus Nephritis
38% of subjects developed nephritis

SLICC Inception cohort, N=1827

Entire Cohort

Lupus Nephritis

ESRD 10.1%

Death 5.9%

Systemic Lupus International Collaborating Clinics
Hanly RG, Rheumatology 2016
Patterns of Renal Disease in Lupus
2003 ISN/RPS Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Freq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal <strong>mesangial</strong> lupus nephritis (LN)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td><strong>Mesangial</strong> proliferative lupus nephritis</td>
<td>10-20%</td>
</tr>
<tr>
<td>Class III</td>
<td><strong>Focal proliferative</strong> lupus nephritis (&lt; 50 % of glomeruli)</td>
<td>10-20%</td>
</tr>
<tr>
<td>Class IV</td>
<td><strong>Diffuse proliferative</strong> lupus nephritis (involving 50% or &gt; glomeruli)</td>
<td>40-60%</td>
</tr>
<tr>
<td>Class V</td>
<td><strong>Membranous</strong> lupus nephritis</td>
<td>10-20%</td>
</tr>
<tr>
<td>Class VI</td>
<td>Advanced <strong>sclerotic</strong> LN (&gt;90% sclerotic glomeruli)</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Immune complex glomerular disease
Renal Abnormalities in Lupus

**Glomerular**
- Mesangial proliferative glomerulonephritis (II) *(mesangial cell)*
- Proliferative glomerulonephritis (III, IV) *(endothelial cell)*
- Lupus membranous nephropathy (V) *(podocyte)*
- Lupus podocytopathy

**Tubulointerstitial**
- Tubulointerstitial nephritis (TBM immune deposits)
- Renal tubular acidosis (hypokalemia, nephrocalcinosis)

**Vascular**
- Thrombotic microangiopathy *(anti-phospholipid antibodies)*
- Lupus vasculopathy (prominent immune deposits)
- Vasculitis (rare)
- Accelerated atherosclerosis (common)
Lupus Podocytopathy

- Class I or II with diffuse effacement of foot processes.
- Described in 18/470 (4%) biopsies in lupus\(^1\)
  - 8/18 nephrotic

**Etiology**
- ? co-existent minimal change disease
- manifestation of lupus

**Responds well to steroid Rx**
- high relapse rate (90%) without maintenance therapy (mycophenolate)\(^2\)

\(^1\)Kraft SW, JASN 2005
\(^2\)Hu WX, Lupus 2015
Discordance between clinical parameters and kidney biopsy$^{1,2}$

6m biopsy$^1$ following induction for proliferative LN
- Patients in clinical remission (Scr stable, proteinuria < 500mg/24), 50% had active renal lesions
- Patients with no evidence of LN activity on biopsy, 62% had proteinuria > 500mg

3.5yrs of treatment$^2$
- Complete clinical responders, 19% had disease activity on repeat biopsy
- Complete histological responders, 42% had proteinuria > 500mg

$^1$Malvar A, NDT 2016
$^2$Alvarado AS, Lupus 2014
What’s new in the treatment of Lupus Nephritis
ACR Treatment Guidelines
Class III / IV Lupus Nephritis

**MMF**
- MMF 2-3 gram a day for 6 months* (preferred to CYC in African Americans and Hispanics)
- PLUS
  - GC IV pulse x 3 days then pred 0.5-1mg/kg per day tapered after a few weeks to lowest effective dose

**CYC**
- CYC
  - PLUS
    - GC IV pulse x 3 days then pred 0.5-1mg/kg per day tapered after a few weeks to lowest effective dose

**ELNT**
- Low Dose
  - 500mg IV every 2 weeks x 6 (for Caucasian of European background)
- OR

**NIH**
- High Dose
  - 500-1000mg mg/M2 BSA i.v. every month x 6

6 mos

**Improved**
- MMF 1-2 g/d OR AZA 2 mg/kg/d +/- low dose daily GC

**Not Improved**
- CYC (low or high) + Pulse GC then daily GC

**Improved**
- Maintenance
  - MMF 1-2g/day OR AZA 2mg/kg/d +/- low dose

**Not Improved**
- Rituximab Or Calcineurin inhibitors + GC

**Improved**
- MMF 1-2g/d OR AZA 2mg/kg/d +/- low dose daily GC

**Not Improved**
- Rituximab Or Calcineurin inhibitors + GC

Hahn BH, Arth Care Res 2012
Anti-B cell Therapy in Lupus Nephritis
Inhibition of B cell function in Lupus Nephritis

Gregersen & Jayne: Nat Rev Nephrol 2012
LUNAR Study: Rituximab

Treatment Period

- Rituximab + MMF (n=72)
- Placebo + MMF (n=72)

Prednisone taper

Weeks 1 and 2 (Days 1 and 15)
Week 16
Weeks 24 and 26 (Days 168 and 182)
Week 52
Week 78

Follow-up Period

= Corticosteroids:
- 1000 mg IV methylprednisolone given at days 1 and then days 2, 3, or 4
- Oral prednisone 0.75 mg/kg/day after IV steroids and tapered to 10 mg/day by d 112

Rovin BH, Arth Rheum 2012
Primary Endpoint:
Renal Response at Week 52

Complete Renal Response (CRR)
Partial Renal Response (PRR)
No Response (NR)

Placebo (N=72)
Rituximab (N=72)

Proportion of Patients

P=0.55*

Mean MMF dose: Placebo: 2.4±0.62 g; Rituximab: 2.7±0.41 g

* Wilcoxon Rank-sum test to compare the proportions of (CRR, PRR, NR) between rituximab and placebo
LUNAR Trial: Conclusions

Primary Endpoint (CR +PR): 57% (Ritux) v 46% (placebo) (NS)

Study Design
- Underpowered, short duration
- Less active disease (less disease resistant to prior Rx)
- Concomitant high dose steroid and high dose MMF (aim 3g bid)

Rituximab may be useful in resistant disease\textsuperscript{1-4}

\textsuperscript{1}Smith KG, Arthritis Rheum 2006
\textsuperscript{2}Pepper R, NDT 2009
\textsuperscript{3}Garcia-Carrasco M, Lupus 2010
\textsuperscript{4}Turner Stokes T, Rheumatology 2011
London, n=50, 12 month F/U

**Clinical**
- Creat 0.9
- Proteinuria 4g/g
- 44% pure Class V (LMN)

**Treatment**
- IVMP 500mg x2,
  **No oral steroid**
- **MMF** 0.5-1.5g bid (per MPA level)
  + **Rituximab** 1g D1 & D15

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**Chart**
- CR 82% at 12m
- PR 62% at 12m

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Condon MB Ann Rheum Dis 2014
RING Study
Rituximab for Lupus Nephritis With Remission as a Goal

**Inclusion**
- Subjects who have failed to achieve complete remission (uP/C > 1g/g) at 6m
- Background MMF or AZA maintenance

**Intervention**

- **Rituximab (1g)**
  - 0w, 2w, 6m, 12m, 24m

- **Control**
CALIBRATE Study
Rituximab + CYC followed by Belimumab

Both Groups

Rituximab 1g x2 (week 0 and 2)
Cytoxan IV 750mg x2 (week 0 and 2)
IVMP 100mg x 2 (week 0 and 2)
Prednisone: 40mg daily → maintenance 10mg

Belimumab (10mg/kg)
4w, 6w, 8w, q4weekly thru week 48

Control

Sponsor: NIAID
Calcineurin Inhibitors
Where do CNIs fit in?
Calcineurin Inhibitors (Cyclosporin, Tacrolimus)

Mechanism of Action

Cyclosporin has direct actions on the podocyte (not via NFAT translocation in T cells)

Multi-target Rx (MMF + Tacrolimus)
Class IV + V Lupus Nephritis

China, n=40, 9 month F/U

Clinical
- Creat 0.9
- Proteinuria 4g/24
- 70% prior Rx with CYC or MMF

Treatment
- IVMP x3, + oral steroid

MMF 1g bid
+ FK 2mg bid (levels 5-7)

IV CYC
NIH protocol

Complete Remission (<0.4g/24)

Bao H, JASN 2008
Multi-target Therapy: MMF + Tacrolimus

**Study (n=362)**
- Prospective RCT
- 26 centers in China
- 6 month

**Inclusion / Exclusion**
- Biopsy within 6m
- No Prior Rx

**Endpoints**
- Complete remission
  - Proteinuria < 0.4g/24h
  - Inactive sediment
  - Normal serum creatinine
- Partial Remission
  - 50%↓ proteinuria (<3.5g/24h)
  - <25% ↑ creatinine

Liu Z, Ann Int Med 2015
Multi-target therapy: Intervention

Both Groups

**IVMP 500mg x 3**

**Prednisone**: 0.6mg/kg 4 weeks, taper by 5mg / week to maintenance 10mg

N=181

**Multi-target**

- MMF 0.5mg BID
- Tacrolimus 2mg BID

N=181

**Cyclophosphamide**

NIH protocol

Liu Z, Ann Int Med 2015
Multi-target Therapy: Results

Remission at 6m

P < 0.001

45.2%

26.5%

Liu Z, Ann Int Med 2015
## Multi-target Therapy: Results

### Appendix Table 2. Comparison of the Complete Remission Incidence Between Multitarget and Intravenous Cyclophosphamide Groups After 24 Weeks of Induction Treatment*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete Remission Incidence (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multitarget</td>
</tr>
<tr>
<td>Overall</td>
<td>45.9 (38.3 to 53.4) (n = 181)</td>
</tr>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>40 (8 to 72) (n = 10)</td>
</tr>
<tr>
<td>Class IV</td>
<td>51 (39 to 64) (n = 74)</td>
</tr>
<tr>
<td>Class V</td>
<td>33 (16 to 50) (n = 32)</td>
</tr>
<tr>
<td>Class III+V</td>
<td>50 (27 to 73) (n = 19)</td>
</tr>
<tr>
<td>Class IV+V</td>
<td>45 (31 to 60) (n = 46)</td>
</tr>
</tbody>
</table>

*Liu Z, Ann Int Med 2015*
## Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Multi-target Rx</th>
<th>IV CYC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>50.3%</td>
<td>52.5%</td>
</tr>
<tr>
<td>Infection</td>
<td>28.2%</td>
<td>25.4%</td>
</tr>
<tr>
<td>GI</td>
<td>12.2%</td>
<td>27%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.6%</td>
<td>6.6%</td>
</tr>
<tr>
<td>SAE</td>
<td>15%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Death (n)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Use of Tacrolimus in Lupus Nephritis

- Fixed dose (2mg BID) versus drug level targets (3-8ng/ml?)
  - Pharmacogenetic markers (CYP3A, MDR1)

- Drug interactions

- Multiple Adverse Effects
  - Nephrotoxicity
  - Hypertension
  - Hyperglycemia
Voclosporin
A new calcineurin inhibitor

- Less plasma variation
  - peak concentration in 2 hours and flat dosing, so you don't have to measure trough levels
- More effective inhibition of calcineurin
- Fewer side effects
- Drug interactions similar
Aura-LV Study
Voclosporin + MMF versus MMF

RCT, n = 265
- Phase IIb
- 20 Countries
- 6 month follow-up

Endpoints
- CR (proteinuria < 500mg)
- PR (proteinuria 50%↓)
- Time to CR & PR

<table>
<thead>
<tr>
<th>Study Demographics</th>
<th>Control</th>
<th>Voclosporin 23.7 mg BID</th>
<th>Voclosporin 39.5 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>88</td>
<td>89</td>
<td>88</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>33 ± 10</td>
<td>31 ± 12</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42 (47.7)</td>
<td>30 (33.7)</td>
<td>36 (40.9)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (5.7)</td>
<td>3 (3.4)</td>
<td>6 (6.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>36 (40.9)</td>
<td>52 (58.4)</td>
<td>44 (50.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (5.7)</td>
<td>4 (4.5)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Biopsy Class (III/IV)</td>
<td>59 (67.0)</td>
<td>56 (62.9)</td>
<td>63 (71.6)</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>100 ± 27</td>
<td>95 ± 28</td>
<td>105 ± 28</td>
</tr>
<tr>
<td>Baseline UPCR</td>
<td>4.4 ± 3.6</td>
<td>5.2 ± 4.2</td>
<td>4.5 ± 3.0</td>
</tr>
<tr>
<td>Death:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

MA Dooley, Arth Rheumatism (abst) 2016
Aura-LV Study
Multi-target therapy: Voclosporin

All Groups

*Prednisone: 20-25mg daily → 5mg (Week 8) → 2.5mg (Week 16-24)
Mycophenolate mofetil: 1g twice daily

N=88
Control

N=89
Voclosporin
Low dose (23.7mg BID)

N=88
Voclosporin
High dose (39.5mg BID)

MA Dooley, Arth Rheumatism (abst) 2016
Aura-LV: Proteinuria Results (24w)
AURA-LV: Results (24w)

Remission Rates (24w)

- Control
- LD VCS
- HD VCS

CR - PR
**AURA-LV: Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>VCS (low dose)</th>
<th>VCS (High dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>50%</td>
<td>56.2%</td>
<td>63.6%</td>
</tr>
<tr>
<td>GI</td>
<td>36.4%</td>
<td>41.6%</td>
<td>52.3%</td>
</tr>
<tr>
<td>SAE</td>
<td>15.8%</td>
<td>25.8%</td>
<td>25%</td>
</tr>
<tr>
<td>Deaths (n)</td>
<td>1</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>
AURA-LV: Results (48w)

Remission Rates (48w)

Control

LD VCS

HD VCS

CR

CR + PR

Parikh SV. NKF 2017 Spring Meetings in Orlando, Florida, April 18-22). Poster 381
Summary
Thank you!